evitable. The average length of life after surgical interference in the malignant gliomas is one to three years. The results in pituitary tumors, by a combination of surgical and x-ray therapy, have been greatly improved in recent years, the relief of general symptoms and the preservation of eyesight being satisfactorily accomplished in fully one-half of the patients.

The results of surgery in the acoustic nerve tumors are good; many of the patients may be relieved of all their symptoms for many years or for the remainder of their natural life.

Can we hope for better results in the future? Much will depend upon the stage at which the disease is recognized and treatment instituted, and if I have succeeded in calling to your attention some of the facts upon which early recognition of tumors of the brain will depend, the purpose of this paper will have been accomplished.

GASTRO-INTESTINAL MANIFESTATIONS OF ALLERGY*

ROBERT A. COOKE

Introduction: The ideas on the intestinal manifestation of allergy, as presented in this paper, have been gained largely from cases with such other sensitizations as asthma, hay fever, urticaria and angioneurotic edema, in which the abdominal allergy was either a part of such a clinical state and due to the same cause or was purely concomitant and due to a specifically unrelated cause. Careful consideration of this material has led me to believe that its presentation and explanation would be of interest to gastro-enterologists and might help them to a better understanding of the allergic nature of certain functional disturbances frequently observed.

*Delivered before a Stated Meeting of the Academy, December 1, 1932.

In the acute allergies, especially well seen in infants sensitive to milk or egg, symptoms such as vomiting, abdominal pain and diarrhœa occur in association with edema of the lips, tongue and pharynx, general urticaria and perhaps asthma. In constitutional reactions following therapeutic injections, as for example, of pollen extracts, vomiting, abdominal distension, pain and diarrhœa may occur as evidences of the general allergic sensitiveness. Such observations bear witness to the fact that the gastro-intestinal tract is capable of allergic reactivity and may be involved in clinical disorders of this type.

The question then arises as to whether we may have clinical examples of allergy with symptoms so strictly or mainly abdominal that they would naturally come under the observation of the gastro-enterologist.

In order to answer this, we will undertake a discussion of the subject by considering:—

1st—Cases presenting symptoms of an acute surgical abdomen.
2nd—Cases presenting symptoms of so-called dyspepsia or indigestion.
3rd—Cases with symptoms of acute gastro-enteritis.
4th—Cases with symptoms of chronic diarrhœa and mucus colitis.

We will then attempt a brief exposition of the types of allergy and finally give some points that may be useful in arriving at a presumptive diagnosis.

1. The Acute Surgical Abdomen. The first case I will cite was reported by Janeway and Mosenthal in 1908 to the Association of American Physicians under the title, "An Unusual Paroxysmal Syndrome, Probably Allied to Recurrent Vomiting, with a Study of the N Metabolism," and was published in the Transactions of that year (p. 504). The diagnosis at that time was toxemia of endogenous origin. The essence of the history there recorded was as follows: A Jewish school-girl aged sixteen years suffered with recurring attacks which began, according to the

mother, when she was two weeks old. In early life the frequency was once a month and the longest period of freedom up to sixteen years was ten weeks. For a year attacks had come weekly and for three months every Friday with absolute periodicity. The attack was described by these authors as having a prodromal period of uneasiness, anorexia and epigastric or abdominal discomfort lasting from four to fourteen hours. Some very mild attacks did not go beyond this stage. Next there was a crescendo period with rapid increase of symptoms, prostration, anorexia, abdominal colic, and also pain referred to shoulders, hips or feet. There was fever, tachycardia and polynuclear leucocytosis. Maximum temperature, 104°; pulse, 140; leucocytes, 28,800. The only differential count recorded when leucocytes were 8,000 showed normal eosinophile count. Occasionally there was headache. The abdomen was rigid, with tenderness at times as extreme as in general peritonitis but varying in the location of maximum sensitiveness, which was usually to one side or the other of the umbilicus. Marked salivation was noted and in severe attacks there was constant nausea and belching and occasional vomiting, the vomitus containing free HCl. This stage lasted from eight to sixteen hours and was followed by the period of recovery with rapid subsidence of pain, then fever and leucocytosis within seventeen hours. She then felt well, had a voracious appetite and within a few days regained the four or five pounds lost in the attack. Gastric analysis showed slight hyperchlorhydria. This case was referred to me in 1916 by Dr. Halpert of Scranton who had originally referred her to Dr. Janeway. The subsequent history was that under later observation by Janeway at Johns Hopkins Hospital an exploratory operation had been done and the appendix removed. It was without effect. The severe attacks continued on the average of twice a month but the milder attacks were more frequent. In spite of this her nutrition remained good. Viewing this case at that time (1916) as a possible manifestation of allergy, the intradermal skin tests were done with such ordinary foodstuffs as milk, egg, cereals, meats and the

important vegetables and fruits. All tests were negative. The family history for allergy was negative. However with the hypothesis that this was allergy and probably an allergy to food, it was a logical conception to exclude at first those foods most commonly taken by a person from infancy to the age of twenty-four, hence milk, eggs and meats were eliminated. The attacks stopped. Milk was subsequently added to the diet on two separate occasions and the well-recognized prodromal symptoms appeared at the end of two or three days. After these two experiences the patient could not again be induced to take milk. When last seen in 1925 she had been free of all attacks. She never touched milk and was not then willing to repeat the experiment. Her two children showed no allergy up to that time. The sudden cessation of attacks of twenty-four years' duration by the withdrawal of milk, and the reproduction of mild attacks on two occasions by the use of milk seem to warrant the diagnosis of an allergy of a type that I will later attempt to explain.

The second case presents even more acute evidences of a possible surgical condition. Mrs. C. B., now sixty-four years old, has no antecedent history of allergy. Her daughter has a condition similar to the one about to be described, but much milder. At about twenty-five years of age she realized that fatty fish gave indigestion with fullness and belching. At the age of forty she began to have frequent severe abdominal attacks which she herself traced to the use of pork fat. Small amounts of lean pork may be eaten without trouble. Fats other than lard in quantity will give headache and dizziness. A typical attack from lard is described as follows: About two to three hours after the fat is eaten the attack begins with abdominal distress which progresses rapidly to pain so severe that she passes into shock. The vomiting is continuous and explosive; pulse rapid; skin pale, cold and clammy. Distension of the abdomen is extreme. Formerly the attack lasted twelve hours. Due to greater care, or loss of sensitivity, the recent attacks have been infrequent and mild. There is no fever. Blood counts have not been made. Tests

with lard by the patch and scratch methods show no evidence of skin sensitiveness. Two years ago this patient had a gallstone attack. There was sudden colicky pain for about half an hour every two or three hours. The entire attack lasted twelve hours and was finally relieved by morphine and atropin. The temperature was 101°. There was rigidity of the right upper quadrant and the gall bladder was palpable for several days. Jaundice was not deep but the stools were clay-colored. The extreme distension, vomiting and collapse symptoms were absent. The patient states that there was a marked difference between this illness and the attacks due to lard.

These two cases represent what at the present time we are wont to regard as angioneurotic edema of the abdominal type. In making a differential diagnosis between this and such surgical conditions as volvulus, strangulated hernia, mesenteric thrombosis or peritonitis, one cannot depend upon temperature or leucocyte count or local abdominal signs. Attention is called to the necessity of discovering any extra-abdominal signs and symptoms such as pain in the extremities (shoulders, hips and feet), headache, salivation and of course the history of repeated attacks, together with other allergies as urticaria and visible angioneurotic edema.

Whether edema of the intestinal wall is a strictly correct conception of the functional pathology is, I believe, a question that cannot be answered. Surgeons who have operated on certain of these cases during an attack report no evident lesion. Adrenalin injections do not give relief, but neither does adrenalin influence the external and visible manifestations of angioneurotic edema to an appreciable extent. Heretofore, we have very largely overlooked the possibility of interpreting these and similar symptoms of intestinal and gastric dysfunction as the result of a disturbance of the sympathetic or parasympathetic divisions of the autonomic system. How such disturbance is created we do not know, for there is no recognized allergy of nerve tissue, but there is no difficulty in conceiving of an edema

indirectly involving the nerves, plexuses or endings and analogous with the cases of cerebral angioneurotic edema.

2. Dyspepsia. Perhaps the most frequent symptom-complex of interest to the gastro-enterologist is that embraced by the term "dyspepsia," in which few or many of the symptoms of pyrosis, eructation, flatulence, hyperacidity, anorexia, fullness after eating, nausea or vomiting are present. To be sure these symptoms may be reflex and due to organic lesions of the appendix, gall bladder or the stomach (ulcer), but in many instances after careful examination they are rightfully attributed to functional disturbances only, and it is to these latter cases we refer.

It is a common experience in taking the histories of cases with asthma and hay fever to elicit also the statement that the patient suffers with indigestion. The gastric symptoms may coincide with the other allergies but more commonly they are unrelated phenomena. The histories of these cases are interesting in that they fall into two groups: First there are those patients who can state that a specific food produces the symptoms of dyspepsia. When eaten the symptoms are quite immediate—within fifteen or twenty minutes. They always occur with great regularity and when tested the skin reaction is quite uniformly positive and confirmatory. The immediateness of the symptoms enables a patient to make the correct diagnosis. These attacks are paroxysmal, abrupt and vary in severity. When such conditions are mild the patients do not consult a physician. They abstain from the offending article. In the second group the symptoms of indigestion are more chronic and more troublesome because the patient cannot relate the trouble to any particular food. I recall one patient, a woman of twenty-five, who in addition to mild urticaria, complained of pyrosis, eructation, fullness and anorexia of six months' duration. The tests in this case were negative. By restrictive diets it was finally determined that the trouble was due to fish taken twice a week. Elimination of fish produced a cessation of both urticaria and dypepsia. When eating fish the symptoms would not

return for several weeks. This case represents the delayed, not the immediate, clinical reaction, hence cause and effect are not obvious to the patient, and where the clinical reaction is delayed, the skin test is always negative. Such cases usually have a threshold of tolerance, and this adds greatly to the difficulty of diagnosis. In this group of delayed allergies with chronic dyspepsia a large number are associated with asthma secondary to sinus infection. The frequency of symptoms of indigestion in association with asthma is well recognized and in this particular group of infective asthma the incidence of associated "dyspepsia" is as high as 30 per cent. One indication that the digestive disorder may be considered as allergy lies in the fact that the proper clearing of infection, where such is possible, produces a cessation of the gastric as well as the bronchial manifestations. This brings up the question of bacterial allergy, which can and does exist and in which gastro-intestinal symptoms may play either a minor part in the allergic symptom-complex or they may dominate the picture. Since it is true that sinus disease may produce both asthma with dyspepsia and asthma without dyspepsia or urticaria or angioneurotic edema without asthma, I believe that the hypothesis is plausible that indigestion without other allergies may be the result of a bacterial allergy, hence consideration must be given to focal infection acting allergically to cause such functional disturbances.

3. Acute Gastro-enteritis. Acute gastro-enteritis with nausea, vomiting and severe diarrhœa may be due to ingested substances, either foods or drugs, and reference is not made here to the ptomaine poisoning from tainted foods. When the onset of symptoms is immediate, that is within an hour of eating, the patient is usually aware of the cause or soon becomes so after several attacks. I recall one instance in which beer was the cause. In such cases skin tests are positive. But in patients with symptoms just as acute in which the interval is longer—a delayed reaction of from four to twelve hours—the patient's diagnosis is less apt to be correct and the difficulty to the physician is greater, for the skin tests will be negative.

When attacks are infrequent and due to some food rarely taken, such as clams, a presumptive diagnosis is easy, and if the patient acquiesces it can be verified by clinical test. But when due to some food commonly taken in which the threshold of tolerance is reasonably great, the clinical procedure of restrictive diets must be resorted to.

4. Chronic Diarrhœa. Mucus Colitis. I have seen a number of cases, usually in connection with other allergies, in which symptoms are never acute and severe but in which either a persistent diarrhœa or symptoms of a so-called mucus colitis were present. In these cases symptoms disappear quite promptly upon avoidance of the specific food. Milk and egg have been found to be the most frequent causative factors. The skin tests are usually negative, for the clinical reaction is delayed. In children particularly, and here again my observations have been in those with an associated allergy, we see a symptom complex not directly related to asthma in which there is marked anorexia, abdominal discomfort rather than pain, with listlessness and fatigueability, with marked evidences of under-nutrition and with looseness of the bowels often alternating with constipation, but with excessive mucus in the stool. I recall a case of asthma due to rabbit dander, in which the symptoms just mentioned were very prominent. The removal of milk from the diet produced a really impressive change in the child's condition with a gain of nearly eight pounds in six months. Such cases are, I believe, analogous to the first case I cited, formerly reported by Janeway, but never so severe, the symptoms being limited to those of the prodromal stage of that case.

We cannot go deeply into an explanation of Allergy but I will briefly sketch our conception of the reactions as they pertain to the cases referred to. In allergy we have many different reactions: Some may be induced artificially and are physiological, as serum disease; some cannot be induced and are natural or spontaneous, as asthma, and rest upon an hereditary or constitutional basis. Pathologically, the reaction may be one of hyperemia, edema, exudation or

inflammation. The clinical symptoms are varied and depend upon the tissue involved in the hypersensitive reaction. Immunologically, the reactions may be immediate or delayed and this point I wish to emphasize, for the usual conception of the allergist is that his function is solely to perform skin tests for diagnosis. As evidenced by the cases cited, this is not so. Many cases of true allergy are not skin sensitive. In hay fever we have allergy in which the clinical symptoms are immediate, that is, they occur within fifteen to sixty minutes of contact. In practically all such cases the skin test is positive. Bear in mind that the positive skin test is itself an immediate reaction and therefore will indicate only the immediate type of clinical reaction. On the other hand, when the clinical symptom is delayed the skin test is negative. In the immediate reactions we find demonstrable antibody in the skin and blood, but in the delayed reaction antibody is not found. In the former case we are testing with the substance for which there is specific antibody. In the latter case we can only assume that the real allergen is some chemical derivative of the apparent allergen and is produced and elaborated within the body hours after it has been introduced. If, for example, in our cases of delayed reaction to milk, it could be determined what this elaborated fraction of milk is, then it is conceivable that the skin test might be positive. But such knowledge still lies beyond our grasp.

Diagnosis. In the matter of diagnosis, then, certain points may be cited that will aid in an assumption of clinical allergy. Since allergy is in many cases a constitutional disorder based upon hereditary influences a careful family history for allergy in the antecedents, both direct and collateral and also in brothers and sisters or even in children, is of value. Of greater importance is the history of other allergies, either past or present, in the patient.

Skin tests should be done in suspected cases for they may give a definite diagnosis, but I have already pointed out and again emphasize the fact that negative skin tests

do not exclude allergy, for positive reactions are not found in those cases with the delayed clinical reaction. In some, eosinophilia is present.

One striking peculiarity of clinical allergy is the frequent repetition of attacks or its distressing chronicity. This is evidenced in practically all the cases cited. Though usually not serious from the standpoint of mortality, allergy may form a serious problem for patient and physician alike unless the cause can be ascertained and removed.

Let us now answer concretely, and I hope in not too unsatisfactory a way, the question asked at the beginning of this paper by saying that gastro-intestinal symptoms do occur as the result of allergies frequently, in my experience, in connection with other allergies, but not necessarily so. The cutaneous tests may help in the diagnosis in a certain percentage of these cases, but to my mind what is even more important is a careful clinical study with the allergic viewpoint in mind.

SIMPLE ACHLORHYDRIC ANEMIA*

NATHAN ROSENTHAL
AND
HAROLD A. ABEL

General Considerations:

In recent years, many articles have been published concerning a type of idiopathic microcytic anemia which has been given various names. The simple achlorhydric anemia of Witts (1), Davies (2), Hare (3), Hurst (4), and Haden (5), the cryptogenic achylic chloranemia of Kaznelson, Reimann and Weiner (6), the primary hypochromic anemia of Dameshek (7), and Waugh (8), the idiopathic hypochromemia of Mills (9), the idiopathic secondary anemia of Watkins (10), the simple achylic anemia

*Delivered before a Stated Meeting of the Academy, December 1, 1932.